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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/789,628	02/27/2004	Ralph M. Ellison	CP380H	7657

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EXAMINER	
PAK, JOHN D	
ART UNIT	**PAPER NUMBER**
1616	

DATE MAILED: 12/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/789,628	ELLISON ET AL.	
	Examiner	Art Unit	
	JOHN PAK	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-12 and 20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-12 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

This Office action is in response to applicant's amendments and remarks of 9/21/2006.

Claims 1, 3-12 and 20 are pending in this application.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-12 and 20 stand rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Zhang (US 6,720,011) and Sacchi et al. in view of CN 1121807 and Shimotsuura et al. for the reasons of record.

Zhang discloses treating lymphoma with arsenic trioxide. See column 1, lines 34-35 and 41-43. Intravenous composition containing 1-10 g arsenic trioxide, sodium chloride and water (column 1, lines 41-54). "[S]trong abruptive effect on the membranes of cancer cells" is disclosed, as well as inhibition of DNA/RNA synthesis (column 1, lines 58-61). Effective daily dose for an adult is disclosed as 10 ml of the composition containing 10 g/l arsenic trioxide added to 500 ml of 10% glucose solution is disclosed. This calculates to about 67 mg/day. Appropriate dose is to be "decreased accordingly for children" (column 2, lines 9-16).

Sacchi et al. teach all-trans retinoic acid (ATRA) in the treatment of various hematological malignancies such as several types of lymphomas (bottom of page 114, right column to top of page 115, left column).

CN 1121807 discloses administering arsenic trioxide as an injection to treat lymphatic cancer (page 4 of the English translation, last paragraph). The formulation of arsenic trioxide is referred to as Ai Ling (see pages 5-6 of the English translation, in particular page 6, last paragraph). Inhibition of DNA/RNA synthesis is disclosed (page 5 of the English translation, lines 6-7).

Shimotsuura et al. disclose that antineoplasmic actions of arsenic trioxide are primarily achieved by DNA composition blockage (page 25 of the English translation, top of page 49 in the original).

Zhang does not explicitly disclose treating lymphoma in a human by administering arsenic in combination with ATRA, optionally with other therapeutic agent(s). However, for the reasons to follow, the claimed invention as a whole would nonetheless have been obvious to the ordinary skilled artisan in this field at the time the invention was made.

Zhang is clear in that arsenic trioxide is effective against "lymphoma." There is no limitation as to the type of lymphoma. Lymphoma is typically a Hodgkin's lymphoma or non-Hodgkin's lymphoma, so inclusion of both would have been obvious to the ordinary skilled artisan. Further, Zhang teaches a strong abruptive effect on the membranes of cancer cells and inhibition of DNA/RNA synthesis. Taken with teachings

of Shimotsuura et al., which confirm the DNA composition blockage action of arsenic trioxide antineoplastic activity and teachings of CN 1121807, which expand on Zhang's teaching of efficacy against lymphoma by teaching efficacy against the broader "lymphatic cancer," the ordinary skilled artisan in this field would have been motivated to administer arsenic trioxide to treat patients with the specific lymphomas recited in the instant claims.

Ionic aqueous solution (applicant's claim 3) is met by the sodium chloride present in the arsenic trioxide solution (Zhang's column 1, lines 44-45). Varying the dose according to the body weight of a human (applicant's claim 12) is met by Zhang's explicit disclosure to decrease the dose for children. The claims are thereby rejected.

As for combined use with ATRA and radiation or other chemotherapeutic agents, such method would have been fairly suggested from the conventional practice in the cancer treatment field to combine the actions and benefits of several therapies to attack the cancer cells from a variety of mechanisms. ATRA is already known to have activity against lymphomas and the therapeutic agents listed in claim 11 are all well-known anti-cancer agents; hence, inclusion of such additional anti-cancer agents in combination with arsenic trioxide and ATRA would have been fairly suggested.

Therefore, the claimed invention, as a whole, would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, because every element of the invention and the claimed invention as a whole have been fairly suggested by the teachings of the cited references.

Applicant's arguments relative hereto have been given due consideration but they were found unpersuasive. Applicant criticizes each of the cited references individually and fails to consider the prior art as a whole.

Applicant argues that the Sacchi article teaches away from combining arsenic trioxide with ATRA. This is a curious argument considering what Sacchi has to say about the retinoid class of compounds and treating lymphomas, "Retinoids, employed as a single agent, have proven useful in the treatment of cutaneous T-cell lymphoma" (page 114, right column, first sentence of last paragraph). Although applicant is critical of the lymphoma treatment study done with ATRA because only 4 patients in 13 achieved partial remission, applicant commits a serious omission in failing to acknowledge that the patients in this study had refractory cutaneous T-cell lymphomas. A treatment that is even partially effective against lymphomas that are resistant to other treatments would have been recognized as an advantageous agent to add to the efficacy of arsenic trioxide. Additionally, applicant criticizes the second study disclosed by Sacchi, but that study was done with patients who had T-cell lymphomas that were known to be resistant to retinoids. There is no single anti-cancer agent that works against all cancer types and resistant forms of cancer exist against even the best of anti-cancer agents. Therefore, the ordinary skilled artisan would not have been taught away by Sacchi's disclosure as applicant argues; rather, he/she would have been motivated to utilize ATRA because it delivers treatment to lymphoma patients who do not respond to other treatments.

Applicant criticizes the Zhang patent for not having a working example of lymphoma treatment but it must be pointed out that neither does applicant's disclosure, i.e. there is no in vivo example in the specification. Further, Zhang is a valid U.S. Patent that claims efficacy of arsenic trioxide against leukemia (claims 1-4) and discloses efficacy against cancers in general and hepatoma and lymphoma in particular (column 1, lines 33-35). Moreover, Zhang teaches that the arsenic trioxide containing composition "exert a strong abruptive effect on the membranes of cancer cells, such as leukemic cells" and inhibits DNA/RNA synthesis (emphases added). Note, Zhang does not limit this teaching to only leukemic cells, as applicant erroneously asserts, because the phrase "such as" is context is exemplary, not limiting.

Relatedly, Shimotsuura et al. disclose that antineoplastic actions of arsenic trioxide are primarily achieved by DNA composition blockage, thereby confirming Zhang's teachings (page 25 of the English translation, top of page 49 in the original). Applicant argues that Shimotsuura's teaching is limited to the tested Sarcoma-180 cell line (soft tissue cancer cells), but the ordinary skilled artisan in this field would not understand the prior art that narrowly. Given the summary of prior art knowledge regarding anticancer activity of arsenic and arsenic trioxide as set forth above, Shimotsuura's disclosure would not be viewed as being limited to sarcoma cancers. The cell line used by Shimotsuura is a commonly used tumor model, and Zhang already confirms that the DNA composition blockage mechanism is present in other cancer cells.

In criticizing CN 1121807, applicant essentially ignores its express teachings and argues only what it does not disclose. CN 1121807 explicitly discloses administering arsenic trioxide as an injection to treat lymphatic cancer (page 4 of the English translation, last paragraph). Inhibition of DNA/RNA synthesis is disclosed (page 5 of the English translation, lines 6-7).

Applicant concludes that there would not have been sufficient motivation to combine ATRA + arsenic trioxide for treating lymphomas because one of ordinary skill in the art would not have been motivated to treat lymphomas with ATRA based on the Sacchi article. For the reasons already stated, the Examiner finds this argument unpersuasive. Applicant fails to address the importance of Sacchi's disclosure that ATRA provided treatment to patients who had lymphomas that were not treatable with other anti-cancer drugs.

Claims 1, 3-12 and 20 stand rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Zhang (US 6,720,011) and Sacchi et al. in view of CN 1121807, Li et al. and Shimotsuura et al.

Zhang, Sacchi et al., CN 1121807 and Shimotsuura et al. are relied on for the same teachings as in the preceding ground of rejection. Discussion of their teachings there is incorporated herein by reference.

Li et al.[1] disclose treating 27 patients with malignant lymphoma, including Hodgkin's disease, with Ailin-1 (see the English translation on page 62). 70.37% remission rate reported (id.).

Li et al. add to the previous discussion of the prior art in that they provide clinical report of 70.37% remission after treating 27 patients with malignant lymphoma, including Hodgkin's disease. The transliteration of Li's chemo-therapeutic formulation is "Ailin-1." From CN 1121807, it is known that "Ai Ling" formulations contain arsenic trioxide. It is the Examiner's position that the ordinary skilled person in the art of treating lymphatic cancers (including those artisans in the U.S. and China) would have recognized various transliterations such as "Ailin-1" and "Ai Ling" to be the same or similar Chinese formulations, which all contain arsenic trioxide.

Hence, Li et al. add to the previously discussed body of knowledge concerning arsenic trioxide and lymphatic cancer efficacy by specifically teaching efficacy against malignant lymphoma, including Hodgkin's disease. In sum, Zhang teaches a strong abruptive effect on the membranes of cancer cells and inhibition of DNA/RNA synthesis. Taken with teachings of Shimotsuura et al., which confirm the DNA composition blockage action of arsenic trioxide antineoplastic activity and teachings of CN 1121807, which expand on Zhang's teaching of efficacy against lymphoma by teaching efficacy against the broader "lymphatic cancer," the ordinary skilled artisan in this field would have been motivated to administer arsenic trioxide to treat patients with the specific

[1] Chinese J. Oncology, Vol. 10, pages 61-62 (1988).

lymphomas recited in the instant claims, particularly in view of Li et al. Additionally, since all of the lymphomas recited in applicant's claims are cancers of the lymphatic system with uncontrolled growth of cells of similar functions and origin, one having ordinary skill in the art would have been motivated to administer arsenic trioxide to treat such lymphomas, particularly in view of its adverse effect on rapid DNA replication.

As for combined use with ATRA and radiation or other chemotherapeutic agents, such method would have been fairly suggested from the conventional practice in the cancer treatment field to combine the actions and benefits of several therapies to attack the cancer cells from a variety of mechanisms. The therapeutic agents listed in claim 11 are all well-known anti-cancer agents and inclusion of such additional anti-cancer agents in combination with arsenic trioxide and ATRA would have been fairly suggested.

Therefore, the claimed invention, as a whole, would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, because every element of the invention and the claimed invention as a whole have been fairly suggested by the teachings of the cited references.

Applicant's arguments relative hereto have been given due consideration but they were found unpersuasive. Applicant adopts the arguments presented with respect to the previous ground of rejection; and as those arguments have been fully addressed above, the discussion there is incorporated herein by reference.

Claims 1, 3-12 and 20 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3-11, 13-17 and 19-20 of copending Application No. 10/649,944 in view of Sacchi et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because of the reasons of record.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant request deferral of the rejection but the rejection can only be maintained or withdrawn. The rejection is maintained because a terminal disclaimer has not been filed.

For these reasons, all claims must be rejected again.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to JOHN PAK whose telephone number is **(571)272-0620.** The Examiner can normally be reached on Monday to Friday from 8 AM to 4:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's SPE, Johann Richter, can be reached on **(571)272-0646**. The fax phone number for the organization where this application or proceeding is assigned is **(571)273-8300**. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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